REMARKS

Claims 1-19, 21, 31, 32, 41-43, 52, 53 and 57-61 were pending in the subject application. Applicants have amended claims 10 and 32. Thus, Claims 1-19, 21, 31, 32, 41-43, 52, 53 and 57-61 are pending in the subject application.

Support for amended claim 32 can be found in the specification inter alia on page 33, lines 28-30, page 34 line 23, and page 35, Table 4.

Restriction

Applicants are pleased to note that the Examiner on page 2 of the December 27, 2005 Office Action rejoined claims 19, 21, 32, 41, 43 and 52 with the product claims under examination. Thus, claims 1-19, 21, 31, 32, 41-43, 52, 53 and 57-61 are now pending and under examination.

Specification

On page 2 of the December 27, 2005 Office Action, the Examiner objected to the disclosure of the subject application because it contains an embedded hyperlink.

In response, Applicants have replaced the paragraph beginning on page 26, line 19 of the subject disclosure in order to remove the embedded hyperlink. Accordingly, Applicants respectfully request that the Examiner withdraw this objection to the specification.

Claim Objections

On page 3 of the December 27, 2005 Office Action, the Examiner objected to claims 41 and 52 as being dependent upon a rejected base claim.

In response, Applicants maintain that claims 1-32 are allowable, for reasons that follow. Accordingly, Applicants respectfully request that the Examiner withdraw this objection to the claims.

Rejection Under 35 U.S.C. §112 - Claims 21, 32 and 43

On page 3 of the December 27, 2005 Office Action, the Examiner rejected claims 21, 32 and 43 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner questioned what is the "predetermined concentration" in step a) of claim 21; and how long is the temperature maintained at -40ºC and -45ºC in step a), what is the "predetermined time" in steps b), d) and e), and what is the reduced pressure that lyophilizes the pharmaceutical composition in step e) of claims 32 and 43.

In response, without conceding the correctness of the Examiner's position, Applicants have amended claim 32 to clarify step e) of the claim. However, Applicants maintain that recitation of the term "predetermined" in claims 21, 32 and 43 is definite. The term "predetermined" is not a relative term. As stated on page 33, lines 8-11 of the subject application, the process of lyophilization may differ according to the percentage of solids in a formulation, thus necessitating adjustments in time and atmospheric conditions. As such, use of the term "predetermined" distinctly claims the subject matter which Applicants regard as the invention.

Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

Double Patenting

On page 5 of the December 27, 2005 Official Action, the Examiner provisionally rejected claims 1-18, 31, 42, 53 and 57-61 under the

doctrine of obviousness-type double patenting as being unpatentable over claims 1-13, 24, 25, 37, 48 and 52 of copending Application No. 10/758,397 (U.S. Patent Application Publication 2005/0008634 A1).

In response, Applicants defer addressing the provisional rejection until copending Application No. 10/758,397 issues, or until the obviousness-type double patenting rejection is the only rejection remaining in the present application. M.P.E.P. §804(I)(B).

Rejections Under 35 U.S.C. §103

Mozes in view of the '856 patent

On pages 5-9 of the December 27, 2005 Office Action, the Examiner maintained the rejection of claims 1-4, 7, 8, 11 and 31 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Application Publication No. 2004/0127408 A1 to Mozes ("Mozes") in view of U.S. Patent No. 5,997,856 to Hora et al. ("the '856 patent").

On pages 3-5 of the December 27, 2005 Office Action, the Examiner extended the rejection under 35 U.S.C. §103(a) to rejoined claims 19 and 21. As such, the following response is in response to the rejections of claims 1-4, 7, 8, 11, 19, 21 and 35.

Applicants' Reply

In response, Applicants respectfully maintain that the present invention is patentable over Mozes in view of the '856 patent.

As will be discussed in detail below, the obviousness rejection of record is fundamentally deficient for failing to explain why prior to Applicants' invention one of skill in the art would look for any solubility enhancing agent for the recited peptide, and select a substituted β-cyclodextrin as a solubility enhancing agent over any

other from the multitude of available solubility-enhancing agents. Neither the June 6, 2005 Office Action nor the December 27, 2005 Office Action squarely answer this question.

Motivation to combine Mozes and the '856 patent is lacking

There exists no motivation to combine Mozes and the '856 patent. As the Examiner recognized on Page 7 of the December 27, 2005 Office Action, "Mozes does disclose modification of the pharmaceutical properties of [a] peptide, such as solubility". The scope of Mozes' modification is limited to salts and chemical derivatives of the peptide, which appear to provide acceptable solubility levels. Mozes does not suggest a need for a separate agent, much less any cyclodextrin, for solubility modification.

Indeed, Mozes makes no reference or even remotely suggest that there is a need to improve the solubility of salt forms of its peptides. Mozes simply does not identify solubility as a problem with any of its peptides in the first place. The peptides are in fact used in the examples of Mozes without any apparent solubility problem. As such, from the disclosure of Mozes, the solubility of its peptides, and certainly of a salt thereof, appear satisfactory.

Thus, absent Applicants' disclosure, there is nothing of record except hindsight motivating the combination of the peptide of Mozes with any solubility enhancer, much less the ones of the '856 patent. This is a fundamental deficiency of the obviousness rejection of record.

Applicants note the Examiner's assertion on page 8 of the December 27, 2005 Office Action that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, which is proper so long as it takes into account knowledge

available at the time the invention was made, and does not include knowledge from Applicants' disclosure. However, the current record fails to identify a suggestion in the prior art to combine the recited peptide with any solubility enhancing agent, much less a cyclodextrin. The current record offers no explanation of why one would look at cyclodextrin art.

Finally, Applicants point out that the issue date of the '856 patent predates the priority date of Mozes. Nonetheless, Mozes does not propose using, nor has any one of skill in the art used, a cyclodextrin for solubilization of the recited peptide. The fact that multiple individuals skilled in the art have not done after several years that which the Examiner now proposes clearly shows the operation of impermissible hindsight.

Selection of cyclodextrin is unexplained

There is no reason of record explaining the selection of cyclodextrin over any other from the multitude of available solubility-enhancing agents. In their own formulation development Applicants tested over forty (40) different solubility enhancers (see pages 23-31 of the subject application) before selecting a cyclodextrin.

In this regard, Applicants point out that cyclodextrins, and specifically beta-cyclodextrins, were known to have less than desirable pharmaceutical properties:

> "The renal toxicity of the parent cyclodextrins is not completely understood. The parent cyclodextrins are reabsorbed and concentrated in the renal tubule where they can interact with and extract cholesterol and other lipid membrane components from cellular structures. A combination of the

> reabsorption and concentration of both the relatively less soluble parent cyclodextrins and the insoluble cyclodextrin/cholesterol complexes may contribute to the demise of cellular integrity. Precipitates of the cyclodextrin or cyclodextrin/cholesterol complexes have been observed during the course of cellular degeneration, but it is unclear how or if they promote the destruction of the cell. [Hepta-(sulfobutyl ether)-β-cyclodextrin] was rationally designed to improve the safety profile of cyclodextrins." Innovative Drug Delivery Technology for Enhance Solubility and Stability, CAPTISOL® Informational Brochure, CyDex, Inc. (2004)(**Exhibit A**)

As such, cyclodextrins would not be the common choice of a solubility enhancer. Therefore, Applicants' selection of a cyclodextrin for enhancing the solubility of the recited peptide is clearly inventive over the prior art.

Even if Mozes and the '856 patent were combined, there was no expectation of success

Nothing more than an "obvious to try" rationale has been presented in support of the rejection of record. Specifically, even assuming *arguendo* the record did contain 1) a motivation to manufacture a pharmaceutical composition with the peptide of Mozes and a solubility enhancer (which the record does not) and 2) there was a reason of record to select a cyclodextrin (which the record does not), one skilled in the art would have no expectation that doing so would result in an acceptable pharmaceutical composition.

Although the '856 patent discloses use of a β-cyclodextrin as a solubility enhancer, the '856 patent shows inconsistent bioactivity of cyclodextrin/protein formulations at physiological pH.

Specifically, two of the three formulations in Table 3 of the '856 patent exhibit lower bioactivity as compared to the protein without cyclodextrin. As such, there could not have been a reasonable expectation of success that the peptide of Mozes would be bioactive if formulated with cyclodextrin.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes and the '856 patent.

Mozes in view of the '856 patent and Anderson et al.

On pages 6-9 of the December 27, 2005 Official Action, the Examiner maintained the rejection of claims 5 and 6 as unpatentable over Mozes in view of the '856 patent as applied to claims 1-4, 7, 8, 11, 31, 42, 53, 57 and 59-61 and in further view of Anderson, B.D. and Flora, K.P. (Chapter 34, pages 739-754, *The Practice of Medicinal Chemistry*, edited by Camilles Georges Wermuth, Academic Press 1996).

Applicants' Reply

In response, Applicants maintain that this rejection suffers from the same deficiencies as the rejection based on Mozes in view of the '856 patent. Anderson et al. fails to remedy any of the deficiencies noted above.

Moreover, the knowledge of what is physiological pH, as provided by Anderson et al., does not teach one how to achieve a pharmaceutical composition at that pH with the recited peptide and the cyclodextrin.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes, the '856 patent and Anderson et al.

Mozes in view of the '856 patent and the '127 patent

On pages 6-9 of the December 27, 2005 Office Action, the Examiner maintained the rejection of claims 9, 10 and 12-18 as unpatentable over Mozes in view of the '856 patent as applied to claims 1-4, 7, 8, 11 and 31 and further in view of U.S. Patent No. 5,134,127 to Stella et al. ("the '127 patent").

The Examiner alleged that the '127 patent discloses the enhanced solubilization, and reduced toxicity of sulfoalkyl ether cyclodextrin derivatives for water insoluble drugs, and therefore a person having ordinary skill in the art would have been motivated and expected to succeed in manufacturing a pharmaceutical composition with a sulfobutyl ether substituted β-cyclodextrin.

Applicants' Reply

In response, Applicants maintain that this rejection suffers from the same deficiencies as the rejection based on Mozes in view of the '856 patent. The '127 patent fails to remedy any of the deficiencies noted above.

Moreover, the '127 patent does not teach how to use a sulfobutyl ether substituted β-cyclodextrin with a peptide. The '127 patent only deals with small molecule compounds. Applicants were the first to show bioactivity of the claimed cyclodextrin/protein formulations at physiological pH (see Table 3 of the subject application).

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes, the '856 patent and the '127 patent.

Summary and Request for Examiner Interview

In view of the remarks made herein, Applicants respectfully maintain that the claimed invention is inventive over the prior art. The obviousness rejection of record is fundamentally deficient for failing to explain why prior to Applicants' invention one of skill in the art would look for any solubility enhancing agent for the recited peptide, and select a substituted β-cyclodextrin as a solubility enhancing agent over any other from the multitude of available solubility-enhancing agents. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

If the Examiner has any questions about the patentability of the pending claims after entry of this Amendment and consideration of the remarks herein, Applicants respectfully request an interview with the Examiner to efficiently advance prosecution. Applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.